Sleep as a model to understand neuroplasticity and recovery after stroke: Observational, perturbational and interventional approaches

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Abstract: Our own experiences with disturbances to sleep demonstrate its crucial role in the recovery of cognitive functions. This importance is likely enhanced in the recovery from stroke; both in terms of its physiology and cognitive abilities. Decades of experimental research have highlighted which aspects and mechanisms of sleep are likely to underlie these forms of recovery. Conversely, damage to certain areas of the brain, as well as the indirect effects of stroke, may disrupt sleep. However, only limited research has been conducted which seeks to directly explore this bidirectional link between both the macro and micro-architecture of sleep and stroke. Here we describe a series of semi-independent approaches that aim to establish this link through observational, perturbational, and interventional experiments. Our primary aim is to describe the methodology for future clinical and translational research needed to delineate competing accounts of the current data. At the observational level we suggest the use of high-density EEG recording, combined analysis of macro and micro-architecture of sleep, detailed analysis of the stroke lesion, and sensitive measures of functional recovery. The perturbational approach attempts to find the causal links between sleep and stroke. We promote the use of transcranial magnetic stimulation combined with EEG to examine the cortical dynamics of the peri-infarct stroke area. Translational research should take this a step further using optogenetic techniques targeting more specific cell populations. The interventional approach focuses on how the same clinical and translational perturbational techniques can be adapted to influence long-term recovery of function.

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Sleep as a model to understand neuroplasticity and recovery after stroke: Observational, perturbational and interventional approaches

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ABSTRACT

Our own experiences with disturbances to sleep demonstrate its crucial role in the recovery of cognitive functions. This importance is likely enhanced in the recovery from stroke; both in terms of its physiology and cognitive abilities. Decades of experimental research have highlighted which aspects and mechanisms of sleep are likely to underlie these forms of recovery. Conversely, damage to certain areas of the brain, as well as the indirect effects of stroke, may disrupt sleep. However, only limited research has been conducted which seeks to directly explore this bidirectional link between both the macro and micro-architecture of sleep and stroke. Here we describe a series of semi-independent approaches that aim to establish this link through observational, perturbational, and interventional experiments. Our primary aim is to describe the methodology for future clinical and translational research needed to delineate competing accounts of the current data. At the observational level we suggest the use of high-density EEG recording, combined analysis of macro and micro-architecture of sleep, detailed analysis of the stroke lesion, and sensitive measures of functional recovery. The perturbational approach attempts to find the causal links between sleep and stroke. We promote the use of transcranial magnetic stimulation combined with EEG to examine the cortical dynamics of the peri-infarct stroke area. Translational research should take this a step further using optogenetic techniques targeting more specific cell populations. The interventional approach focuses on how the same clinical and translational perturbational techniques can be adapted to influence long-term recovery of function.

1. Introduction

In adults, stroke is the first cause of permanent disability and the third cause of mortality. Major advances have been made in stroke prevention and in the management of acute stroke (e.g. thrombolysis, treatment in stroke units). Conversely, recovery from stroke can be promoted by training and exercise (neurorehabilitation) but pharmacological solutions seem to be limited (Dobkin, 2008). Currently, functional outcome still depends largely on the initial conditions of the lesion: location, severity and extension.

Stroke leads to disruption of cortical and subcortical circuits adjacent to the damaged area. Recovery is related to the reorganization and reallocation of lost functions toward spared neurons that had been mainly devoted to other activities. Our understanding of the nature of this neuroplasticity process has greatly improved over the last 2–3 decades. Animal and human data suggest that this functional remapping may related to changes in brain excitability in the peri-infarct area and distant connected areas (Gerloff et al., 2006; Murphy and Corbett, 2009; Nudo, 2013). Animal studies suggest that these changes stem from increased GABAergic and glutamatergic transmission, the pharmacological reduction of the former and excitation of the latter can improve functional recovery (Clarkson et al., 2010; Song et al., 2017). Human studies have shown that ipsi- and contralesional cortical areas undergo changes in their activation, as assessable both at the cortical level by functional neuroimaging and at the cortico-spinal level by mean of transcranial magnetic stimulation (TMS), which parallel post-stroke functional recovery (Gerloff et al., 2006). In addition, modulation of the contralesional cortical areas by TMS has been shown to

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reduce post-stroke cognitive disability and improve activities of daily living (Cazzoli et al., 2012). These observations support the hypothesis that training and exercise performed during neurorehabilitation promote recovery through a use-dependent neuroplasticity process of relearning and functional remapping.

Every day experience reminds us of the crucial role that sufficient, quality sleep plays in the recovery of our own cognitive and physical abilities. Furthermore, local sleep, by means of an increase in *slow wave activity* (SWA) in delimited portions of the cortex has been found to increase following a cognitive task involving that brain region during preceding wakefulness (Huber et al., 2004; Hung et al., 2013). These local changes are also seen in structural and diffusion weighted magnetic resonance imaging (Bernardi et al., 2016); as well as positron emission tomography (Maquet, 2000). Conversely, local reduction of slow waves by closed loop acoustic stimulation leads to a reduction in the learning capacity associated with that particular cortical area (Fattinger et al., 2017). At the macrosleep-scale, optogenetic disruption of sleep continuity impairs memory consolidation in mice (Rolls et al., 2011). Therefore, the same use-dependent mechanisms which drive changes in sleep architecture may underlie the neuroplasticity found during recovery from stroke.

While sleep likely plays a key role in successful recovery, the structural and functional changes after stroke also have the potential to negatively impact sleep. In a recent meta-analysis of 15 studies, Baglioni et al., (2016), found a consistent reduction in the total amount of time acute stroke patients were asleep, further compounded with a reduction in sleep efficiency during that reduced sleep period. Interestingly, no consistent differences were reported for changes in REM sleep, furthering highlighting the specific link between stroke and NREM; in particular SWA (however see Pace et al., 2018, for translational evidence of REM changes). Further studies also suggest that beyond the direct impact on sleep, acute patients may have a higher prevalence of sleep-disordered breathing (Camilo et al., 2016; Huhtakangas et al., 2017). This would typically lead to a decrease in total sleep time, increase in sleep fragmentation, and a corresponding decrease in SWA. Sleep loss would also have the indirect effect of increasing daytime sleepiness, lowering the ability and motivation to optimally perform the tasks required for active rehabilitation of function (Gooneratne et al., 2003; Frohnhofen et al., 2013). Overall, the current state of research suggests a tight, bi-directional link between sleep and stroke. Both in terms of the effect of stroke on specific aspects of the macro and micro-architecture of sleep, as well as the potential of sleep to act as the direct and modulating driver of recovery. Understanding how brain damage, its consequences on brain activity, recovery, and sleep are interrelated is of outstanding interest for both the scientific community and society in general.

Here we describe a series of semi-independent approaches that aim to firmly establish this link through both observational and interventional experiments. Our primary aim is to describe the methodology for future research needed to delineate competing accounts of the current data. In doing so we identify key projects needed to establish the critical role of specific aspects of sleep as the mechanism of functional impairment and as an interventional tool for its recovery. Importantly, while each of the described approaches gives us a piece of the puzzle, they each contribute to the other's explanatory and predictive roles. For each approach we describe the key missing pieces to our current understanding, the methodological rationale of future work to directly address these limitations, and the challenges each may face. In particular, we outline 3 related hypotheses: that the local damage following stroke leads to local changes in sleep architecture; that these local effects on slow waves are likely to be split into both beneficial effects of slow waves ('good waves'), and those which underlie the functional impairment ('bad waves'); and that the functional recovery following stroke can be monitored and assessed by tracking these changes in sleep architecture.

2. Observational approach

The first logical starting place for examining the relationship between sleep and stroke is its passive measurement. While most previous studies have relied on clinical polysomnography to record sleep, we recommend the use of high-density EEG (hd-EEG) to make significant progress in the field. Current setups of as high as 256-channel nets can be applied relatively quickly, and additional measurements (e.g. ECG, leg movements, respiration), can be performed synchronously. Such setups are particularly advantageous to examine the microarchitecture of sleep, and track the local changes expected following focal damage after stroke. The use of the high-density array allows us to track the extent of local changes to sleep, and makes the average reference a plausible solution to the referencing problem of low-density EEG montages (Dien, 1998; Lei and Liao, 2017). Macroarchitecture analysis would also benefit by having additional channels by which to score sleep stages; especially in the case where local distortions of EEG activity make scoring difficult.

One hd-EEG study reported increased slow-wave activity directly over the infarct area in both sleep and wake, yet decreased activity in the adjacent perilesional area which persisted into the chronic period of recovery (Poryazova et al., 2015). Another study demonstrated the link between highly local slow-wave activity and recovery of function in a group of chronic aphasia patients (Sarasso et al., 2014). These limited examples demonstrate the unique utility of hd-EEG in stroke patients, as well as the importance of longitudinal measures as the neural activity in sleep is likely to change along with the neuroplasticity associated with recovery. Repeated measurement from acute to chronic stages would also be useful in distinguishing the direct effect of the persistent structural damage and those changes that relate to the functional recovery. These studies show that hd-EEG recordings are feasible in these patients and clinical settings.

Slow activity during wakefulness in the area of the stroke lesion has been consistently reported for decades (Nuwer, 1996; Yokoyama et al., 1996; Murri et al., 1998; Fernández-Bouzas et al., 2002). Decreases in these waking slow-waves predict a positive clinical outcome (Finnigan et al., 2004, 2007). Yet whether this activity and that of slow wave sleep are closely related remains unclear. This *confusion* is at least partly due to the fact that these phenomena have been mostly captured using spectral power analysis. With the advent of hdEEG measures and novel analytical approaches, we are now in a position to detect and analyse properties of individual slow waves (Riedner et al., 2007; Mensen et al., 2016). This approach can distinguish between several independent properties of the individual waves such as incidence, amplitude, slopes, topographic location and extension, and travelling parameters of each wave (Massimini et al., 2004). The pathological slow waves during wakefulness are likely also present during sleep, yet are masked by the appearance of normal slow waves. In depth analysis at the individual wave level of each of the wave property may be able to better characterise and distinguish the normal, *good*, from pathological, *bad*, waves. Doing so would shed new light into whether these pathological waves underlie the functional impairments in acute patients, or whether they represent similar recovery processes as those in normal sleep. Perhaps most interestingly is whether these two seemingly distinct avenues in fact represent different sides of the same coin. That is, the slow waves causing initial functional impairment are necessary for acute recovery and stabilisation, yet their persistence into chronic stages represent long-term disability. Determining the properties that separate these two processes is necessary for adequate future interventional approaches that seek may seek to reduce those waves that lead to impairment, while promoting only those necessary for neural recovery.

Given the diversity of functional impairments and its clear relationship to lesion location, we should expect a similar diversity in predicting distinct effects on sleep. Therefore a key element of future research should be detailed description, segmentation and analysis of

stroke lesion. While the majority of papers cited in a recent meta-analysis described the lesion location in some basic form (e.g. hemisphere, infra vs supra tentorial), relatively few of the studies segmented the lesion using the clinical MRI (whether automatic or manually; Maier et al., 2017). Fewer still included such measures as direct predictors of sleep impairment. Several parameters can be obtained that would plausibly have an impact on sleep structure such as precise location, volume, and severity (Müller et al., 2002). More secondary parameters from the segmentation process could also be explored such as the white/grey damage ratio which may affect distinct aspects of individual waves (e.g. grey matter damage may affect wave amplitude through local synchronisation; white matter damage may block slow wave travelling). Seeing that the clinical MRI is almost always available, future work could also benefit from using specific sequences or imaging techniques to gain further insights on the impact of the lesion (e.g. diffusion tensor imaging Song et al., 2015; or functional connectivity, Hallam et al., 2018).

2.1. Measuring functional recovery

However interesting the link between sleep and stroke may be at the basic science level, at the clinical level the utility of this link is bounded by its further relationship to functional recovery. That is, the applicability of even a well-established link between the two phenomenon would be limited if the variability in these factors were not then significantly related to either prediction of functional outcome or subsequent clinical treatment possibilities. Correlational analysis of the functional recovery with the parameters of slow wave activity could further differentiate the patterns of neurophysiological activity which are inherent to the neuroplasticity associated with the recovery of function (i.e. “good waves”), from those which underlie the loss of function in the first place (i.e. “bad waves”). Such an analysis could be performed on both the short-term scale comparing functional recovery measures before and after a single night of sleep. However, recovery from the acute to subacute timescales is likely to be more revealing.

Studies should therefore ensure that measures of functional recovery are integrated into the same research protocol and designed to be sufficiently sensitive to detect even small changes. Given the range of possible functional impairments, research with stroke patients must grapple with the trade-off between the personalisation of functional tasks necessary to achieve this sufficient sensitivity and broader cognitive tasks applied at the group level so that results are generalisable. Further consideration must be given to the amount of time-on-task, especially in the acute stage, such that the accuracy of the functional measures are not undermined by fatigue or lack of motivation in the patient population. In translational work, standardised behavioural tests such as the ladder walking test (Cummings et al., 2007), beam balance test (Lang et al., 2011), or single pellet reaching (Farr and Whishaw, 2002), can overcome some of these concerns. Yet, even the simple handling of the animals can be a significant stress factor, require multiple and larger groups of animals, as well as being time consuming for the researcher.

In this context, we recommend two overlapping approaches: (semi-) automatisation of tasks and continuous passive measurement. In clinical work, the former can be achieved through the use of computer-based tasks to evaluate cognitive performance, ideally in the form of simple and short, tablet-based activities using a touch-screen. On the surface this may seem to undermine the importance of the patient-researcher interaction, however, this liberates the investigator from the routine performance of the task in hand and allows them to interact more directly with the patient. Furthermore, this allows for a standardisation of tasks, and the automatic measurement of additional parameters of interest. For example, the digital adaptation of the classic test for spatial working memory, the corsi-block test, allows for precise presentation timing, multiple randomised trials, and inter-block reaction time measurements (Brunetti et al., 2014). For passive measures, actigraphy can be used to continually track the sleep/wake rhythm but also has the potential to also track motor recovery (Cavalcanti et al., 2012; Bakken et al., 2014). More vision-related deficits, especially neglect, may actually be best measured through the use of passive and continuous eye-tracking (Müri et al., 2009; Delazer et al., 2018); thus fulfilling both the need for increased sensitivity and automaticity in measuring functional recovery.

Automation of animal behavioural tasks reduces direct animal contact and experimenter time per animal, which further reduces disruption to their normal sleep rhythms (Fenrich et al., 2015; Wong et al., 2016). For example, an automated single pellet reaching task, enabled in the animal’s *home-cage* produced improved learning curves and increased trial numbers as compared to the traditional version of the task (Fenrich et al., 2015) while allowing synchronized optogenetic interventions (Ellens et al., 2016) as well as electrophysiological monitoring. Recent advances in automatic scoring and analysis of animal movement from regular video sources could further add to the sensitivity of motor recovery while allowing for the continuous analysis over longer time periods (Mathis et al., 2018). Therefore, automation of behavioural tasks for translational stroke research will aid to study more specific outcome measures for new types of interventions, while increasing feasibility and reducing animal stress.

3. Perturbational approach

The observational approaches described above would provide profound, but ultimately correlative, insights into the relationship between sleep and stroke. To parallel observational approaches, the relationship between sleep and stroke could be observed from a causal perspective by studying effective connectivity of thalamo-cortical system employing a perturbational approach (Massimini et al., 2009). One possibility is to perturb the thalamo-cortical system through sensory stimuli, and several studies have examined auditory, somatosensory and visual evoked potentials during sleep showing a decrease of the late components in the evoked sensory responses (Bastuji and García-Larrea, 1999; Kakigi et al., 2003). However, peripheral evoked potentials may be insensitive indicators in the context of a damaged brain after stroke becausethe cortical area of interest may have become disconnected or impaired. These confounds can be avoided by employing transcranial magnetic stimulation combined with EEG (TMS/EEG) This technique allows for direct stimulation of different subsets of cortical neurons and measures, with good spatial-temporal resolution, the effects on the rest of the thalamocortical system (Ilmoniemi et al., 1997). In this way, it is possible to bypass sensory inputs and to directly probe, non-invasively, the response of the cortical area of interest (Massimini et al., 2009).

Recent TMS/EEG studies have shown a prominent impairment in the ability of cortical circuits to sustain complex patterns of activity following brain injury (Rosanova et al., 2012). Crucially, in the present context, this impairment extends beyond the anatomical disconnection and seems to be due to the engagement of pathological, sleep-like neuronal behavior; namely, the occurrence of cortical OFF-periods. A recent study employing intracortical single pulse electrical stimulation (SPES) and simultaneous local field potential (LFP) recordings in humans during NREM sleep (Pigorini et al., 2015), showed that the tendency of cortical neurons to fall into an OFF-period (i.e. down- state in cortical neurons - Steriade et al., 1993; Timofeev et al., 2000) is the key mechanism that disrupts the chain of causal interactions among distant cortical areas.further. Although the mechanism of OFF-period following brain injury is still to be elucidated, both in vivo and in vitro studies showed that these silent periods may result from increased K-currents (Compte et al., 2003; Englot et al., 2010; Lemieux et al., 2014), from alterations of the balance between excitation and inhibition (Murase et al., 2004) and from partial cortical deafferentation (Nita et al., 2007; Timofeev et al., 2000). All these mechanisms are associated with brain lesions, impairing information transmission by inducing *bistability* in portions of the thalamocortical system that are otherwise healthy

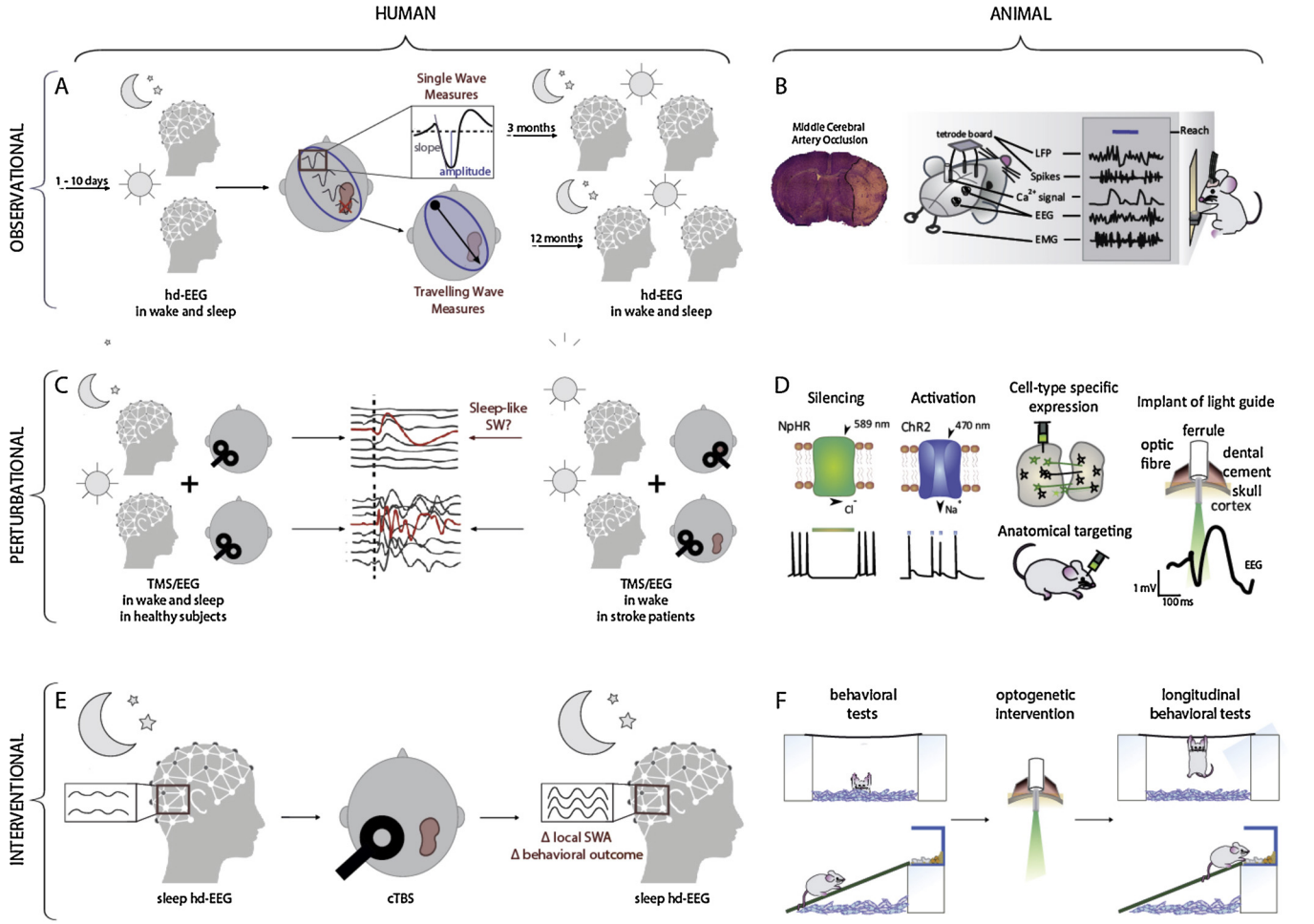

Fig. 1. Three different, parallel approaches for studying the link between sleep and stroke. Red areas on topographies represent stroke lesions. **Observational: A.** Longitudinal hd-EEG measures in human stroke patients during wakefulness and sleep after 3 and 12 months from the baseline measures. **B.** Local Field Potential, Spikes, Ca^{++}, EEG and EMG analysis in animal model of stroke, made by Middle Cerebral Artery Occlusion as in the next two approaches. **Perturbational: C.** Triggering, in human subjects and by means of TMS/EEG, complex responses during wakefulness and slow waves during sleep (*Left*) and comparing them to the response evoked by TMS in stroke patients while stimulating perilesional or contralesional areas (*Right*). **D.** Triggering slow waves in animal model of stroke by means of optogenetic stimulations. *Left*, NpHR and ChR2 genes chosen for the silencing or the activation of Cl^- and Na^+ currents respectively. *Middle*, Specific cell-type expression and target inclusion in the animal. *Right,* Light guide implant in the animal that triggers slow waves. **Interventional: E.** Longitudinal assessment in humans: hd-EEG measures during sleep before and after cTBS treatment in human stroke patient over contralesional cortical areas. **F.** Longitudinal assessment in animal model of stroke: behavioural tests before and after optogenetic intervention (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

(Fig. 1C). In line with this view, a recent TMS/EEG study showed that the residual cerebral cortex of unresponsive wakefulness syndrome patients (UWS) with multi-focal brain lesions fails to engage in complex patterns of activity because neurons tend to fall into a pathological OFF-period after an initial activation. (Rosanova et al., 2012, 2018). In both the EEG and LFP time series, these off-periods present as slow waves, visually indistinguishable from those found in NREM sleep (Massimini et al., 2007).

Future studies employing TMS/EEG should test whether a similar pathological, sleep-like dynamic may play a role in focal brain lesions, including the ones due to stroke. If this is the case, it will be important to deepen our understanding of the mechanistic link between sleep-like slow wave activity, OFF-periods and brain lesion. Indeed, to the extent that sleep-like dynamics represent the common functional endpoint of brain lesion, detecting its presence and tracking its evolution over time may offer a valuable read-out to devise, guide and titrate therapeutic strategies aimed at functional recovery after stroke. To this aim, one possibility is a translational study in which intracranial stimulation and recording in humans during NREM sleep, typically those in presurgical evaluation for epileptic activity (Cossu et al., 2005), is paralleled by animal studies, both during NREM sleep and after stroke, employing similar stimulation and recording parameters.

It remains an open question, as to whether the slow-wave-like activity found in perilesional neuronal populations after stroke, especially those that seem to reflect functional impairment (i.e. *bad waves*), show distinct activity neurophysiological profiles, to those during NREM sleep which relate to recovery of function (e.g. *good waves*). Perturbational approaches in animal models offer reproducible experimental conditions to test for slow wave activity (Fig. 1D). Intracranial electrical stimulation in mice has been used to evoke cortical slow waves that show comparable properties to endogenous slow waves (Vyazovskiy et al., 2009). Experimental animal models can elucidate the roles of genetically identified and anatomically defined cell populations for regulating cortical SWA. For example, chemogenetic activation of somatostatin cortical interneurons, using the Designer-Receptor-Activated-by-Designer-Drug (DREADD) approach increased SWA, while their chemogenetic silencing reduced SWA in mice (Funk et al., 2016). In contrast, activation of parvalbumin positive interneurons reduced slow-wave activity, while triggering short OFF periods (Funk et al., 2017).

Optogenetic stimulation offers the time precision of electrical intracranial stimulation and TMS, but with the additional ability to perturb only genetically specified cell populations. A recent study optogenetically activated somatostatin or parvalbumin containing cortical interneurons to induce immediate transitions from cortical up to cortical down states (Zucca et al., 2017). Comparison of optogenetically induced slow waves could teach us about the mechanisms behind naturally occurring slow waves and how they are similar to those produced through perturbation. Optogenetic stimulation can be readily applied to mice that have undergone an experimental stroke. Thus specific targeting of neuronal cell types may aid in promoting the beneficial, recovery aspects of these "good" slow waves, while minimising their negative effects on normal brain functioning of "bad" slow waves.

4. Interventional approach

The "perturb-and-measure" approach described above can probe specific features of the thalamo-cortical system by means of single-pulse electrical or magnetic brain stimulation. Interestingly, by changing stimulation parameters we can move from a perturbational to an interventional approach. Repetitive stimulation has the potential to alter the physiology and functional organization of the brain beyond the duration of the stimulation (Esser et al., 2006; Peinemann et al., 2004; Quartarone et al., 2005). To date, there are several demonstrations that repetitive application of TMS (rTMS) can produce longer-lasting effects, both inhibitory and excitatory depending on stimulation parameters, and thus offer potential for clinical applications post-stroke (Lefaucheur et al., 2014). Various studies have assessed the effect of rTMS on motor domains (Chang et al., 2010; Conforto et al., 2012; Emara et al., 2009, 2010; Fregni et al., 2006; Liepert et al., 2007; Mansur et al., 2005; Meehan et al., 2011; Takeuchi et al., 2008), post-stroke aphasia (Hamilton et al., 2010; Kakuda et al., 2010; Martin et al., 2009, 2004, Naeser et al., 2011, 2005b, 2005a) and neglect, significantly reducing the typical right-side bias in attention (Cazzoli et al., 2012; Koch et al., 2008; Nyffeler et al., 2009).

Importantly, in healthy individuals, high-frequency rTMS applied to motor cortex induced localized potentiation of TMS-evoked cortical EEG responses in wake, while also increasing slow wave activity during subsequent sleep (Huber et al., 2007). This study raises the critical question of the role that subsequent sleep may have in the long-term consolidation of the beneficial effects of potential rTMS intervention in stroke patients. Given the efficacy that contralesional, inhibitory rTMS has already shown in the neglect patients, we suggest using this as a model to examine the relationship between the scale of functional recovery and changes to local sleep architecture in both the ipsi and contralateral regions before and after rTMS (Fig. 1E). As with most recent studies in neuromodulation we recommend the use of theta-burst stimulation protocols, a particular form of rTMS which enables the use of lower stimulation strength, shorter total stimulation time, while actually improving the reliability and duration of the offline effects (Huang et al., 2005). Given the current literature, it is plausible that the long-term amelioration of neglect symptoms after rTMS intervention largely depend on the quality and structure of subsequent sleep.

The effects of non-invasive brain stimulation is likely to derive from modulation of at long-term potentiation (LTP)-like or long-term depression (LTD)-like processes at the neuronal level (Huang et al., 2007). However, the precise mechanisms of post-stroke recovery may be difficult to understand in human research alone. A variety of stroke animal models have been developed and successfully used in stroke research to elucidate a cascade of events and mechanisms that follow the ischemic insult (Carmichael, 2005; Fluri et al., 2015). Animal models allow a controlled, homogeneous and reproducible stroke size, as well as the potential for including specific anatomical areas within the lesion (Fig. 1B, left). To date such invasive investigation of pathophysiological processes or vasculature analysis can not be replaced by in *in-vitro* preparations. The interventional approach in stroke animal models through optogenetics allows the exploration of numerous stimulation paradigms and time flexibility, crucial aspects often limited within the clinical research field (Fig. 1F). Conversely, the wide range of manipulations that optogenetic provides, could render the identification of the best paradigm particularly challenging. Nevertheless, optogenetic stimulation in stroke animal models has already been shown beneficial for recovery of function (Cheng et al., 2014; Daadi et al., 2016; Shah et al., 2017; Tennant et al., 2017; Wahl et al., 2017). Thus, via direct manipulation of specific neuronal networks and investigating the effect on functional outcome we can better understand which cell types drive post-stroke recovery. With this information we can improve stimulation patterns, as well as identify potential targets for stroke therapies. To date however, modulation of sleep oscillations through optogenetics has never been attempted in animal models of stroke. One valid and translational approach would be to evoke sleep-like local mechanisms by mimicking spontaneous slow oscillations through either activation or silencing of specific neuronal subpopulations (see section on perturbational approaches above). Such stimulation could then be used to rescue or enhance micro and macro sleep-phenotypes in stroke models and to specifically elucidate the role of sleep-like activity for functional recovery and plasticity.

5. Conclusions

Understanding how brain damage, its consequences on brain activity and brain repair are interrelated, is still an unmet goal in clinical neuroscience. Thus, the demonstration that sleep related processes may play a role in neuroplasticity and functional outcome after stroke could represent an advancement *per se*. To this aim we proposed in the present work a multi-modal methodological approach that merge the potential of various standard approaches. In particular we suggest that, integrating different parallel experimental procedures, including observational, perturbational and interventional experiments, both in human and animal models, could be promising, and the integrated result is likely to exceed those obtained by the sum of the individual approaches alone.

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References

Baglioni, C., Nissen, C., Schweinoch, A., Riemann, D., Spiegelhalder, K., Berger, M., Weiller, C., Sterr, A., 2016. Polysomnographic characteristics of sleep in stroke: a systematic review and meta-analysis. PLoS One 11, e0148496. https://doi.org/10.1371/journal.pone.0148496.

Bakken, Linda N., Kim, HesookSuzie, Finset, Arnstein, Lerdal, Anners, 2014. Subjective sleep quality in relation to objective sleep estimates: comparison, gender differences and changes between the acute phase and the six-month follow-up after stroke. J. Adv. Nurs. 70 (March (3)), 639–650. https://doi.org/10.1111/jan.12228.

Bastuji, H., García-Larrea, L., 1999. Evoked potentials as a tool for the investigation of human sleep. Sleep Med. Rev. 3, 23–45.

Bernardi, G., Cecchetti, L., Siclari, F., Buchmann, A., Yu, X., Handjaras, G., Bellesi, M., Ricciardi, E., Kecskemeti, S.R., Riedner, B.A., Alexander, A.L., Benca, R.M., Ghilardi, M.F., Pietrini, P., Cirelli, C., Tononi, G., 2016. Sleep reverts changes in human gray and white matter caused by wake-dependent training. Neuroimage 129, 367–377. https://doi.org/10.1016/j.neuroimage.2016.01.020.

Brunetti, Riccardo, Gatto, Claudia Del, Delogu, Franco, 2014. ECorsi: Implementation and Testing of the Corsi Block-Tapping Task for Digital Tablets. Front. Psychol. 5 (September). https://doi.org/10.3389/fpsyg.2014.00939.

Camilo, M.R., Schnitman, S.V., Sander, H.H., Eckeli, A.L., Fernandes, R.M.F., Leite, J.P., Bassetti, C.L., Pontes-Neto, O.M., 2016. Sleep-disordered breathing among acute ischemic stroke patients in Brazil. Sleep Med. 19, 8–12. https://doi.org/10.1016/j.sleep.2015.11.008.

Carmichael, S.T., 2005. Rodent models of focal stroke: size, mechanism, and purpose. NeuroRx 2, 396–409. https://doi.org/10.1602/neurorx.2.3.396.

Cavalcanti, Paula, Campos, Tania, Araujo, John, 2012. Actigraphic analysis of the sleep-wake cycle and physical activity level in patients with stroke: implications for clinical practice. Chronobiol. Int. 29 (November (9)), 1267–1272. https://doi.org/10.3109/07420528.2012.719960.

Cazzoli, D., Müri, R.M., Schumacher, R., von Arx, S., Chaves, S., Gutbrod, K., Bohlhalter, S., Bauer, D., Vanbellingen, T., Bertschi, M., Kipfer, S., Rosenthal, C.R., Kennard, C., Bassetti, C.L., Nyffeler, T., 2012. Theta burst stimulation reduces disability during the activities of daily living in spatial neglect. Brain 135, 3426–3439. https://doi.org/10.1093/brain/aws182.

Chang, W.H., Kim, Y.-H., Bang, O.Y., Kim, S.T., Park, Y.H., Lee, P.K.W., 2010. Long-term effects of rTMS on motor recovery in patients after subacute stroke. J. Rehab. Med. 42, 758–764. https://doi.org/10.2340/16501977-0590.

Cheng, M.Y., Wang, E.H., Woodson, W.J., Wang, S., Sun, G., Lee, A.G., Arac, A., Fenno, L.E., Deisseroth, K., Steinberg, G.K., 2014. Optogenetic neuronal stimulation promotes functional recovery after stroke. Proc. Natl. Acad. Sci. U. S. A. 111, 12913–12918. https://doi.org/10.1073/pnas.1404109111.

Clarkson, A.N., Huang, B.S., Macisaac, S.E., Mody, I., Carmichael, S.T., 2010. Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. Nature 468, 305–309. https://doi.org/10.1038/nature09511.

Compte, A., Sanchez-Vives, M.V., McCormick, D.A., Wang, X.-J., 2003. Cellular and network mechanisms of slow oscillatory activity (< 1 Hz) and wave propagations in a cortical network model. J. Neurophysiol. 89, 2707–2725. https://doi.org/10.1152/jn.00845.2002.

Conforto, A.B., Anjos, S.M., Saposnik, G., Mello, E.A., Nagaya, E.M., Santos, W., Ferreiro, K.N., Melo, E.S., Reis, F.I., Scaff, M., Cohen, L.G., 2012. Transcranial magnetic stimulation in mild to severe hemiparesis early after stroke: a proof of principle and novel approach to improve motor function. J. Neurol. 259, 1399–1405. https://doi.org/10.1007/s00415-011-6364-7.

Cossu, M., Cardinale, F., Castana, L., Citterio, A., Francione, S., Tassi, L., Benabid, A.L., Lo Russo, G., 2005. Stereoelectroencephalography in the presurgical evaluation of focal epilepsy: a retrospective analysis of 215 procedures. Neurosurgery 57, 706–718 discussion 706-718.

Cummings, B.J., Engesser-Cesar, C., Cadena, G., Anderson, A.J., 2007. Adaptation of a ladder beam walking task to assess locomotor recovery in mice following spinal cord injury. Behav. Brain Res. 177, 232–241. https://doi.org/10.1016/j.bbr.2006.11.042.

Daadi, M.M., Klausner, J.Q., Bajar, B., Goshen, I., Lee-Messer, C., Lee, S.Y., Winge, M.C.G., Ramakrishnan, C., Lo, M., Sun, G., Deisseroth, K., Steinberg, G.K., 2016. Optogenetic Stimulation of Neural Grafts Enhances Neurotransmission and Downregulates the Inflammatory Response in Experimental Stroke Model. Cell Transplant. 25, 1371–1380. https://doi.org/10.3727/096368915X688533.

Delazer, Margarete, Sojer, Martin, Ellmerer, Philipp, Boehme, Christian, Benke, Thomas, 2018. Eye-tracking provides a sensitive measure of exploration deficits after acute right MCA stroke. Front. Neurol. 9 (June). https://doi.org/10.3389/fneur.2018.00359.

Dien, Joseph, 1998. Issues in the application of the average reference: review, critiques, and recommendations. Behav. Res. Methods 30 (March (1)), 34–43. https://doi.org/10.3758/bf03209414.

Dobkin, B.H., 2008. Training and exercise to drive poststroke recovery. Nat. Clin. Pract. Neurol. 4, 76–85. https://doi.org/10.1038/ncpneuro0709.

Ellens, D.J., Gaidica, M., Toader, A., Peng, S., Shue, S., John, T., Bova, A., Leventhal, D.K., 2016. An automated rat single pellet reaching system with high-speed video capture. J. Neurosci. Methods 271, 119–127. https://doi.org/10.1016/j.jneumeth.2016.07.009.

Emara, T., El Nahas, N., Elkader, H.A., Ashour, S., El Etrebi, A., 2009. MRI can predict the response to therapeutic repetitive transcranial magnetic stimulation (rTMS) in stroke patients. J. Vasc. Interv. Neurol. 2, 163–168.

Emara, T.H., Moustafa, R.R., Elnahas, N.M., Elganzoury, A.M., Abdo, T.A., Mohamed, S.A., Eletribi, M.A., 2010. Repetitive transcranial magnetic stimulation at 1Hz and 5Hz produces sustained improvement in motor function and disability after ischaemic stroke. Eur. J. Neurol. 17, 1203–1209. https://doi.org/10.1111/j.1468-1331.2010.03000.x.

Englot, D.J., Yang, L., Hamid, H., Danielson, N., Bai, X., Marfeo, A., Yu, L., Gordon, A., Purcaro, M.J., Motelow, J.E., Agarwal, R., Ellens, D.J., Golomb, J.D., Shamy, M.C.F., Zhang, H., Carlson, C., Doyle, W., Devinsky, O., Vives, K., Spencer, D.D., Spencer, S.S., Schevon, C., Zaveri, H.P., Blumenfeld, H., 2010. Impaired consciousness in temporal lobe seizures: role of cortical slow activity. Brain 133, 3764–3777. https://doi.org/10.1093/brain/awq316.

Esser, S.K., Huber, R., Massimini, M., Peterson, M.J., Ferrarelli, F., Tononi, G., 2006. A direct demonstration of cortical LTP in humans: a combined TMS/EEG study. Brain Res. Bull. 69, 86–94. https://doi.org/10.1016/j.brainresbull.2005.11.003.

Farr, T.D., Whishaw, I.Q., 2002. Quantitative and qualitative impairments in skilled reaching in the mouse (Mus musculus) after a focal motor cortex stroke. Stroke 33, 1869–1875.

Fenrich, K.K., May, Z., Hurd, C., Boychuk, C.E., Kowalczewski, J., Bennett, D.J., Whishaw, I.Q., Fouad, K., 2015. Improved single pellet grasping using automated ad libitum full-time training robot. Behav. Brain Res. 281, 137–148. https://doi.org/10.1016/j.bbr.2014.11.048.

Fernández-Bouzas, A., Harmony, T., Fernández, T., Aubert, E., Ricardo-Garcell, J., Valdés, P., Bosch, J., Casián, G., Sánchez-Conde, R., 2002. Sources of abnormal EEG activity in spontaneous intracerebral hemorrhage. Clin. Electroencephalogr. 33, 70–76.

Finnigan, S.P., Rose, S.E., Walsh, M., Griffin, M., Janke, A.L., McMahon, K.L., Gillies, R., Strudwick, M.W., Pettigrew, C.M., Semple, J., Brown, J., Brown, P., Chalk, J.B., 2004. Correlation of quantitative EEG in acute ischemic stroke with 30-day NIHSS score: comparison with diffusion and perfusion MRI. Stroke 35, 899–903. https://doi.org/10.1161/01.STR.0000122622.73916.d2.

Finnigan, S.P., Walsh, M., Rose, S.E., Chalk, J.B., 2007. Quantitative EEG indices of sub-acute ischaemic stroke correlate with clinical outcomes. Clin. Neurophysiol. 118, 2525–2532. https://doi.org/10.1016/j.clinph.2007.07.021.

Fluri, F., Schuhmann, M.K., Kleinschnitz, C., 2015. Animal models of ischemic stroke and their application in clinical research. Drug Des. Devel. Ther. 9, 3445–3454. https://doi.org/10.2147/DDDT.S56071.

Fregni, F., Boggio, P.S., Valle, A.C., Rocha, R.R., Duarte, J., Ferreira, M.J.L., Wagner, T., Fecteau, S., Rigonatti, S.P., Riberto, M., Freedman, S.D., Pascual-Leone, A., 2006. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke 37, 2115–2122. https://doi.org/10.1161/01.STR.0000231390.58967.6b.

Frohnhofen, H., Popp, R., Frohnhofen, K., Fulda, S., 2013. Impact of daytime sleepiness on rehabilitation outcome in the elderly. Adv. Exp. Med. Biol. 755, 103–110. https://doi.org/10.1007/978-94-007-4546-9_14.

Funk, C.M., Honjoh, S., Rodriguez, A.V., Cirelli, C., Tononi, G., 2016. Local slow waves in superficial layers of primary cortical areas during REM sleep. Curr. Biol. 26, 396–403. https://doi.org/10.1016/j.cub.2015.11.062.

Funk, C.M., Peelman, K., Bellesi, M., Marshall, W., Cirelli, C., Tononi, G., 2017. Role of somatostatin-positive cortical interneurons in the generation of sleep slow waves. J. Neurosci. 37, 9132–9148. https://doi.org/10.1523/JNEUROSCI.1303-17.2017.

Gooneratne, N.S., Weaver, T.E., Cater, J.R., Pack, F.M., Arner, H.M., Greenberg, A.S., Pack, A.I., 2003. Functional outcomes of excessive daytime sleepiness in older adults. J. Am. Geriatr. Soc. 51, 642–649.

Gerloff, C., Bushara, K., Sailer, A., Wassermann, E.M., Chen, R., Matsuoka, T., Waldvogel, D., Wittenberg, G.F., Ishii, K., Cohen, L.G., Hallett, M., 2006. Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after capsular stroke. Brain 129, 791–808. https://doi.org/10.1093/brain/awh713.

Hallam, G.P., Thompson, H.E., Hymers, M., Millman, R.E., Rodd, J.M., Lambon Ralph, M.A., Smallwood, J., Jefferies, E., 2018. Task-based and resting-state fMRI reveal compensatory network changes following damage to left inferior frontal gyrus. Cortex 99, 150–165. https://doi.org/10.1016/j.cortex.2017.10.004.

Hamilton, R.H., Sanders, L., Benson, J., Faseyitan, O., Norise, C., Naeser, M., Martin, P., Coslett, H.B., 2010. Stimulating conversation: enhancement of elicited propositional speech in a patient with chronic non-fluent aphasia following transcranial magnetic stimulation. Brain Lang. 113, 45–50. https://doi.org/10.1016/j.bandl.2010.01.001.

Huang, Ying-Zu, Edwards, Mark J., Rounis, Elisabeth, Bhatia, Kailash P., Rothwell, John C., 2005. Theta burst stimulation of the human motor cortex. Neuron 45 (January (2)), 201–206. https://doi.org/10.1016/j.neuron.2004.12.033.

Huang, Ying-Zu, Chen, Rou-Shayn, Rothwell, John C., Wen, Hsin-Yi, 2007. The after-effect of human Theta burst stimulation is NMDA receptor dependent. Clin. Neurophysiol. 118 (May (5)), 1028–1032. https://doi.org/10.1016/j.clinph.2007.01.021.

Huber, R., Ghilardi, M.F., Massimini, M., Tononi, G., 2004. Local sleep and learning. Nature 430, 78–81. https://doi.org/10.1038/nature02663.

Huber, R., Esser, S.K., Ferrarelli, F., Massimini, M., Peterson, M.J., Tononi, G., 2007. TMS-induced cortical potentiation during wakefulness locally increases slow wave activity during sleep. PLoS One 2, e276. https://doi.org/10.1371/journal.pone.0000276.

Huhtakangas, J.K., Huhtakangas, J., Bloigu, R., Saaresranta, T., 2017. Prevalence of sleep apnea at the acute phase of ischemic stroke with or without thrombolysis. Sleep Med. 40, 40–46. https://doi.org/10.1016/j.sleep.2017.08.018.

Hung, C.-S., Sarasso, S., Ferrarelli, F., Riedner, B., Ghilardi, M.F., Cirelli, C., Tononi, G., 2013. Local experience-dependent changes in the wake EEG after prolonged wakefulness. Sleep 36, 59–72. https://doi.org/10.5665/sleep.2302.

Ilmoniemi, R.J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H.J., Näätänen, R., Katila, T., 1997. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. Neuroreport 8, 3537–3540.

Kakigi, R., Naka, D., Okusa, T., Wang, X., Inui, K., Qiu, Y., Tran, T.D., Miki, K., Tamura, Y., Nguyen, T.B., Watanabe, S., Hoshiyama, M., 2003. Sensory perception during sleep in humans: a magnetoencephalograhic study. Sleep Med. 4, 493–507.

Kakuda, W., Abo, M., Uruma, G., Kaito, N., Watanabe, M., 2010. Low-frequency rTMS with language therapy over a 3-month period for sensory-dominant aphasia: case series of two post-stroke Japanese patients. Brain Inj. 24, 1113–1117. https://doi.org/10.3109/02699052.2010.494587.

Koch, G., Oliveri, M., Cheeran, B., Ruge, D., Lo Gerfo, E., Salerno, S., Torriero, S., Marconi, B., Mori, F., Driver, J., Rothwell, J.C., Caltagirone, C., 2008. Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect. Brain 131, 3147–3155. https://doi.org/10.1093/brain/awn273.

Lang, C.E., Bland, M.D., Connor, L.T., Fucetola, R., Whitson, M., Edmiaston, J., Karr, C., Sturmoski, A., Baty, J., Corbetta, M., 2011. The brain recovery core: building a system of organized stroke rehabilitation and outcomes assessment across the continuum of care. J. Neurol. Phys. Ther. 35, 194–201. https://doi.org/10.1097/NPT.0b013e318235dc07.

Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S.S., Baeken, C., Benninger, D.H., Cantello, R.M., Cincotta, M., de Carvalho, M., De Ridder, D., Devanne, H., Di Lazzaro, V., Filipović, S.R., Hummel, F.C., Jääskeläinen, S.K., Kimiskidis, V.K., Koch, G., Langguth, B., Nyffeler, T., Oliviero, A., Padberg, F., Poulet, E., Rossi, S., Rossini, P.M., Rothwell, J.C., Schönfeldt-Lecuona, C., Siebner, H.R., Slotema, C.W., Stagg, C.J., Valls-Sole, J., Ziemann, U., Paulus, W., Garcia-Larrea, L., 2014. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. 125, 2150–2206. https://doi.org/10.1016/j.clinph.2014.05.021.

Lei, Xu, Liao, Keren, 2017. Understanding the influences of EEG reference: a large-scale brain network perspective. Front. Neurosci. 11. https://doi.org/10.3389/fnins.2017.00205.

Lemieux, M., Chen, J.-Y., Lonjers, P., Bazhenov, M., Timofeev, I., 2014. The impact of cortical deafferentation on the neocortical slow oscillation. J. Neurosci. 34, 5689–5703. https://doi.org/10.1523/JNEUROSCI.1156-13.2014.

Liepert, J., Zittel, S., Weiller, C., 2007. Improvement of dexterity by single session low-frequency repetitive transcranial magnetic stimulation over the contralesional motor cortex in acute stroke: a double-blind placebo-controlled crossover trial. Restor. Neurol. Neurosci. 25, 461–465.

Maier, O., Menze, B.H., von der Gablentz, J., Ḧani, L., Heinrich, M.P., Liebrand, M., Winzeck, S., Basit, A., Bentley, P., Chen, L., Christiaens, D., Dutil, F., Egger, K., Feng, C., Glocker, B., Götz, M., Haeck, T., Halme, H.-L., Havaei, M., Iftekharuddin, K.M., Jodoin, P.-M., Kamnitsas, K., Kellner, E., Korvenoja, A., Larochelle, H., Ledig, C., Lee, J.-H., Maes, F., Mahmood, Q., Maier-Hein, K.H., McKinley, R., Muschelli, J., Pal, C., Pei, L., Rangarajan, J.R., Reza, S.M.S., Robben, D., Rueckert, D., Salli, E., Suetens, P.,

Wang, C.-W., Wilms, M., Kirschke, J.S., Kr Amer, U.M., Münte, T.F., Schramm, P., Wiest, R., Handels, H., Reyes, M., 2017. ISLES 2015 - A public evaluation benchmark for ischemic stroke lesion segmentation from multispectral MRI. Med. Image Anal. 35, 250–269. https://doi.org/10.1016/j.media.2016.07.009.

Mathis, A., Mamidanna, P., Cury, K.M., Abe, T., Murthy, V.N., Mathis, M.W., Bethge, M., 2018. DeepLabCut: markerless pose estimation of user-defined body parts with deep learning. Nat. Neurosci. 21, 1281. https://doi.org/10.1038/s41593-018-0209-y.

Mansur, C.G., Fregni, F., Boggio, P.S., Riberto, M., Gallucci-Neto, J., Santos, C.M., Wagner, T., Rigonatti, S.P., Marcolin, M.A., Pascual-Leone, A., 2005. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 64, 1802–1804. https://doi.org/10.1212/01.WNL.0000161839.38079.92.

Maquet, P., 2000. Functional neuroimaging of normal human sleep by positron emission tomography. J. Sleep Res. 9, 207–231.

Martin, P.I., Naeser, M.A., Theoret, H., Tormos, J.M., Nicholas, M., Kurland, J., Fregni, F., Seekins, H., Doron, K., Pascual-Leone, A., 2004. Transcranial magnetic stimulation as a complementary treatment for aphasia. Semin. Speech Lang. 25, 181–191. https://doi.org/10.1055/s-2004-825654.

Martin, P.I., Naeser, M.A., Ho, M., Doron, K.W., Kurland, J., Kaplan, J., Wang, Y., Nicholas, M., Baker, E.H., Alonso, M., Fregni, F., Pascual-Leone, A., 2009. Overt naming fMRI pre- and post-TMS: two nonfluent aphasia patients, with and without improved naming post-TMS. Brain Lang. 111, 20–35. https://doi.org/10.1016/j.bandl.2009.07.007.

Massimini, M., Huber, R., Ferrarelli, F., Hill, S., Tononi, G., 2004. The sleep slow oscillation as a traveling wave. J. Neurosci. 24, 6862–6870. https://doi.org/10.1523/JNEUROSCI.1318-04.2004.

Massimini, Marcello, Ferrarelli, Fabio, Esser, Steve K., Riedner, Brady A., Huber, Reto, Murphy, Michael, Peterson, Michael J., Tononi, Giulio, 2007. Triggering sleep slow waves by transcranial magnetic stimulation. Proc. Natl. Acad. Sci. U. S. A. 104 (May (20)), 8496–8501. https://doi.org/10.1073/pnas.0702495104.

Massimini, M., Boly, M., Casali, A., Rosanova, M., Tononi, G., 2009. A perturbational approach for evaluating the brain's capacity for consciousness. Prog. Brain Res. 177, 201–214. https://doi.org/10.1016/S0079-6123(09)17714-2.

Meehan, S.K., Linsdell, M.A., Handy, T.C., Boyd, L.A., 2011. Interhemispheric enhancement of somatosensory cortical excitability through contralateral repetitive transcranial magnetic stimulation. Clin. Neurophysiol. 122, 1637–1644. https://doi.org/10.1016/j.clinph.2011.01.002.

Mensen, A., Riedner, B., Tononi, G., 2016. Optimizing detection and analysis of slow waves in sleep EEG. J. Neurosci. Methods 274, 1–12. https://doi.org/10.1016/j.jneumeth.2016.09.006.

Müller, C., Achermann, P., Bischof, M., Nirkko, A.C., Roth, C., Bassetti, C.L., 2002. Visual and spectral analysis of sleep EEG in acute hemispheric stroke. Eur. Neurol. 48, 164–171. https://doi.org/10.1159/000065509.

Murase, N., Duque, J., Mazzocchio, R., Cohen, L.G., 2004. Influence of interhemispheric interactions on motor function in chronic stroke. Ann. Neurol. 55, 400–409. https://doi.org/10.1002/ana.10848.

Müri, RenéM., Cazzoli, D., Nyffeler, T., Pflugshaupt, T., 2009. Visual Exploration Pattern in Hemineglect. Psychol. Res. 73 (March (2)), 147–157. https://doi.org/10.1007/s00426-008-0204-0.

Murphy, T.H., Corbett, D., 2009. Plasticity during stroke recovery: from synapse to behaviour. Nat. Rev. Neurosci. 10, 861–872. https://doi.org/10.1038/nrn2735.

Murri, L., Gori, S., Massetani, R., Bonanni, E., Marcella, F., Milani, S., 1998. Evaluation of acute ischemic stroke using quantitative EEG: a comparison with conventional EEG and CT scan. Neurophysiol. Clin. 28, 249–257. https://doi.org/10.1016/S0987-7053(98)80115-9.

Naeser, M.A., Martin, P.I., Nicholas, M., Baker, E.H., Seekins, H., Helm-Estabrooks, N., Cayer-Meade, C., Kobayashi, M., Theoret, H., Fregni, F., Tormos, J.M., Kurland, J., Doron, K.W., Pascual-Leone, A., 2005a. Improved naming after TMS treatments in a chronic, global aphasia patient–case report. Neurocase 11, 182–193. https://doi.org/10.1080/13554790590944663.

Naeser, M.A., Martin, P.I., Nicholas, M., Baker, E.H., Seekins, H., Kobayashi, M., Theoret, H., Fregni, F., Maria-Tormos, J., Kurland, J., Doron, K.W., Pascual-Leone, A., 2005b. Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. Brain Lang. 93, 95–105. https://doi.org/10.1016/j.bandl.2004.08.004.

Naeser, M.A., Martin, P.I., Theoret, H., Kobayashi, M., Fregni, F., Nicholas, M., Tormos, J.M., Steven, M.S., Baker, E.H., Pascual-Leone, A., 2011. TMS suppression of right pars triangularis, but not pars opercularis, improves naming in aphasia. Brain Lang. 119, 206–213. https://doi.org/10.1016/j.bandl.2011.07.005.

Nita, D.A., Cissé, Y., Timofeev, I., Steriade, M., 2007. Waking-sleep modulation of paroxysmal activities induced by partial cortical deafferentation. Cereb. Cortex 17, 272–283. https://doi.org/10.1093/cercor/bhj145.

Nudo, R.J., 2013. Recovery after brain injury: mechanisms and principles. Front. Hum. Neurosci. 7, 887. https://doi.org/10.3389/fnhum.2013.00887.

Nuwer, M.R., 1996. Quantitative EEG analysis in clinical settings. Brain Topogr. 8, 201–208.

Nyffeler, T., Cazzoli, D., Hess, C.W., Müri, R.M., 2009. One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. Stroke 40, 2791–2796. https://doi.org/10.1161/STROKEAHA.109.552323.

Pace, Marta, Camilo, Millene R., Seiler, Andrea, Duss, Simone B., Mathis, Johannes, Manconi, Mauro, Bassetti, Claudio L., 2018. Rapid Eye Movements Sleep as a Predictor of Functional Outcome after Stroke: A Translational Study. Sleep 41 (October (10)). https://doi.org/10.1093/sleep/zsy138.

Peinemann, A., Reimer, B., Löer, C., Quartarone, A., Münchau, A., Conrad, B., Roman Siebner, H., 2004. Long-lasting increase in corticospinal excitability after 1800 pulses of subthreshold 5 Hz repetitive TMS to the primary motor cortex. Clin. Neurophysiol. 115, 1519–1526. https://doi.org/10.1016/j.clinph.2004.02.005.

Pigorini, A., Sarasso, S., Proserpio, P., Szymanski, C., Arnulfo, G., Casarotto, S., Fecchio, M., Rosanova, M., Mariotti, M., Lo Russo, G., Palva, J.M., Nobili, L., Massimini, M., 2015. Bistability breaks-off deterministic responses to intracortical stimulation during non-REM sleep. Neuroimage 112, 105–113. https://doi.org/10.1016/j.neuroimage.2015.02.056.

Poryazova, R., Huber, R., Khatami, R., Werth, E., Brugger, P., Barath, K., Baumann, C.R., Bassetti, C.L., 2015. Topographic sleep EEG changes in the acute and chronic stage of hemispheric stroke. J. Sleep Res. 24, 54–65. https://doi.org/10.1111/jsr.12208.

Quartarone, A., Bagnato, S., Rizzo, V., Morgante, F., Sant'Angelo, A., Battaglia, F., Messina, C., Siebner, H.R., Girlanda, P., 2005. Distinct changes in cortical and spinal excitability following high-frequency repetitive TMS to the human motor cortex. Exp. Brain Res. 161, 114–124. https://doi.org/10.1007/s00221-004-2052-5.

Riedner, B.A., Vyazovskiy, V.V., Huber, R., Massimini, M., Esser, S., Murphy, M., Tononi, G., 2007. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. Sleep 30, 1643–1657.

Rolls, A., Colas, D., Adamantidis, A., Carter, M., Lanre-Amos, T., Heller, H.C., de Lecea, L., 2011. Optogenetic disruption of sleep continuity impairs memory consolidation. Proc. Natl. Acad. Sci. U. S. A. 108, 13305–13310. https://doi.org/10.1073/pnas.1015633108.

Rosanova, M., Gosseries, O., Casarotto, S., Boly, M., Casali, A.G., Bruno, M.-A., Mariotti, M., Boveroux, P., Tononi, G., Laureys, S., Massimini, M., 2012. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. Brain 135, 1308–1320. https://doi.org/10.1093/brain/awr340.

Rosanova, M., Fecchio, M., Casarotto, S., Sarasso, S., Casali, A.G., Pigorini, A., Comanducci, A., Seregni, F., Devalle, G., Bodart, O., Boly, M., Gosseries, O., Laureys, S., Massimini, M., 2018. Sleep-like bistability, loss of causality and complexity in the brain of Unresponsive Wakefulness Syndrome patients. Nat. Commun. 9–4427. https://doi.org/10.1038/s41467-018-06871-1.

Sarasso, S., Määttä, S., Ferrarelli, F., Poryazova, R., Tononi, G., Small, S.L., 2014. Plastic changes following imitation-based speech and language therapy for aphasia a high-density sleep EEG study. Neurorehabil. Neural Repair 28, 129–138. https://doi.org/10.1177/1545968313498651.

Shah, A.M., Ishizaka, S., Cheng, M.Y., Wang, E.H., Bautista, A.R., Levy, S., Smerin, D., Sun, G., Steinberg, G.K., 2017. Optogenetic neuronal stimulation of the lateral cerebellar nucleus promotes persistent functional recovery after stroke. Sci. Rep. 7, 46612. https://doi.org/10.1038/srep46612.

Song, J., Nair, V.A., Young, B.M., Walton, L.M., Nigogosyan, Z., Remsik, A., Tyler, M.E., Farrar-Edwards, D., Caldera, K.E., Sattin, J.A., Williams, J.C., Prabhakaran, V., 2015. DTI measures track and predict motor function outcomes in stroke rehabilitation utilizing BCI technology. Front. Hum. Neurosci. 9, 195. https://doi.org/10.3389/fnhum.2015.00195.

Song, M., Yu, S.P., Mohamad, O., Cao, W., Wei, Z.Z., Gu, X., Jiang, M.Q., Wei, L., 2017. Optogenetic stimulation of glutamatergic neuronal activity in the striatum enhances neurogenesis in the subventricular zone of normal and stroke mice. Neurobiol. Dis. 98, 9–24. https://doi.org/10.1016/j.nbd.2016.11.005.

Steriade, M., Contreras, D., Curró Dossi, R., Nuñez, A., 1993. The slow (< 1 Hz) oscillation in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation in interacting thalamic and neocortical networks. J. Neurosci. 13, 3284–3299.

Takeuchi, N., Tada, T., Toshima, M., Chuma, T., Matsuo, Y., Ikoma, K., 2008. Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranical magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. J. Rehabil. Med. 40, 298–303. https://doi.org/10.2340/16501977-0181.

Tennant, K.A., Taylor, S.L., White, E.R., Brown, C.E., 2017. Optogenetic rewiring of thalamocortical circuits to restore function in the stroke injured brain. Nat. Commun. 8, 15879. https://doi.org/10.1038/ncomms15879.

Timofeev, I., Grenier, F., Bazhenov, M., Sejnowski, T.J., Steriade, M., 2000. Origin of slow cortical oscillations in deafferented cortical slabs. Cereb. Cortex 10, 1185–1199.

Vyazovskiy, V.V., Faraguna, U., Cirelli, C., Tononi, G., 2009. Triggering slow waves during NREM sleep in the rat by intracortical electrical stimulation: effects of sleep/wake history and background activity. J. Neurophysiol. 101, 1921–1931. https://doi.org/10.1152/jn.91157.2008.

Wahl, A.S., Büchler, U., Brändli, A., Brattoli, B., Musall, S., Kasper, H., Ineichen, B.V., Helmchen, F., Ommer, B., Schwab, M.E., 2017. Optogenetically stimulating intact rat corticospinal tract post-stroke restores motor control through regionalized functional circuit formation. Nat. Commun. 8, 1187. https://doi.org/10.1038/s41467-017-01090-6.

Wong, C.W., DeYoung, P.N., Liu, T.T., 2016. Differences in the resting-state fMRI global signal amplitude between the eyes open and eyes closed states are related to changes in EEG vigilance. Neuroimage 124, 24–31. https://doi.org/10.1016/j.neuroimage.2015.08.053.

Yokoyama, E., Nagata, K., Hirata, Y., Satoh, Y., Watahiki, Y., Yuya, H., 1996. Correlation of EEG activities between slow-wave sleep and wakefulness in patients with supratentorial stroke. Brain Topogr. 8, 269–273.

Zucca, S., D'Urso, G., Pasquale, V., Vecchia, D., Pica, G., Bovetti, S., Moretti, C., Varani, S., Molano-Mazón, M., Chiappalone, M., Panzeri, S., Fellin, T., 2017. An inhibitory gate for state transition in cortex. Elife 6. https://doi.org/10.7554/eLife.26177.